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Multiple Myeloma of the Liver Presenting as Nonobstructive Jaundice

To the Editor: The clinical manifestations in multiple myeloma are usually due to bone-tissue invasion by tumor and to the presence in serum and/or urine of a monoclonal immunoglobulin. Extraosseous involvement by myeloma is frequently found at autopsy [1], but it is clinically manifest in few patients [2]. We report on a case of multiple myeloma involving the liver, presenting as nonobstructive jaundice.

A 76-year-old man was referred to our hospital in October 1993 because of weakness, weight loss, and gastrointestinal hemorrhage. Physical examination showed somnolence, jaundice, and hepatomegaly 4 cm below the costal margin. Laboratory studies showed: hemoglobin 9.7 g/dl, platelets 80×10^9/l, prothrombin index 57%, creatinine 2.35 mg/dl, calcium 12 mg/dl, total protein 7.2 g/dl, bilirubin 8.1 mg/dl, GGT 248 IU/l (normal, 10–45 IU/l), alkaline phosphatase 397 IU/l (normal, 100–280 IU/l), and lactate deshydrogenase 155 IU/l (normal to 460 IU/l). Serum protein studies revealed an M-component Ig A-Kappa of 3.9 g/dl. Serological tests were negative for hepatitis B and C viruses. A bone-marrow aspirate was performed, showing a 90% of atypical plasma cells. Radiograph films revealed osteoporosis and multiple lytic lesions. Abdominal CT scan showed hepatomegaly and ascitis. Neither biliary dilatation nor tumor nodules were seen. A diffuse sinusoidal infiltration of the liver by plasma cells was demonstrated in an ultrasound-guided biopsy (Fig. 1A). Plasma-cell immunostaining with heavy- and light-chain antibodies showed alpha and kappa restriction (Fig. 1B). The patient was treated with melphalan and prednisone daily for 4 days every 4–6 weeks. After two courses of this treatment he was asymptomatic, and his serum bilirubin and alkaline phosphatase returned near to normal. An objective response was documented after six melphalan and prednisone courses. Thereafter, he continued to receive chemotherapy in the same schedule until November 1994. He did well until February 1995 when anemia, azotemia, hepatomegaly, and an increase of plasma cells in bone marrow were noted. After a transitory response to a second-line chemotherapy regimen he died, 22 months after diagnosis.

Myelomatous infiltration of extraosseous tissues is relatively frequent (two thirds of patients) in autopsy series, including direct spread from osseous disease and distant organ involvement [1]. The spleen, liver, and lymph nodes are the most common sites of distant involvement.

Extraosseous manifestations are found in <5% of patients with multiple myeloma. Enlarged lymph nodes and skin lesions are the most frequent findings [2]. Myeloma causing jaundice has occasionally been reported in the literature. Usually, this has been due to biliary obstruction by a myelomatous mass in the head of the pancreas [3]. Since nonobstructive jaundice was the predominant clinical manifestation in our patient, we performed an invasive procedure confirming the diffuse monoclonal plasma-cell infiltration of the liver. As far as we know, only one case of liver dysfunction due to diffuse plasma-cell infiltration has been confirmed by biopsy [4].

Extraosseous manifestations have usually been reported in young patients with an aggressive form of myeloma that is characterized by rapid progression, resistance to treatment, and a median survival of 1.5 months [5]. In contrast, our case had an excellent response to a standard treatment regimen and a longer survival than expected. Moreover, features associated with the "aggressive" disease were not seen in our patient: he was 76 years old and had neither elevated serum levels of lactate deshydrogenase nor fever unrelated to infection.

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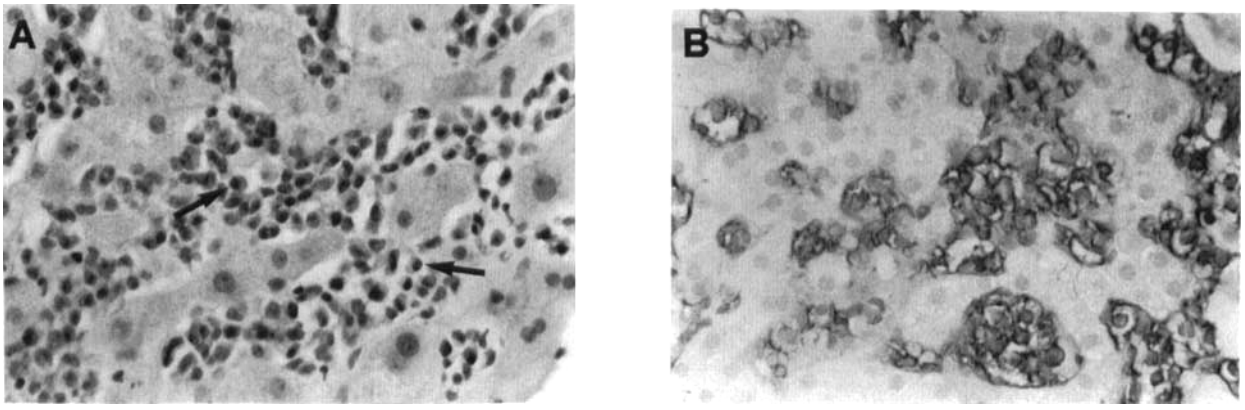

Fig. 1. A: Histologic study of liver. Note expansion of sinusoidal spaces diffusely infiltrated by plasma cells (arrows) (H&E, ×125). B: Liver parenchyma stained with kappa light chain showing extensive involvement of sinusoidal spaces (paraffin section immunoperoxidase, ×125).

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Transfusion-Induced Hypoxemia in Beta-Thalassaemia

To the Editor: Thalassaemic patients frequently present cardiomyopathy; some of them are in a hypoxic state, and they have defective oxygen unloading. In this setting, any additive hypoxemia may lead to deleterious effects. Some authors [1] reported a dramatic drop of PaO_2 (mean 22 mm Hg, range 0–70 mm Hg) following blood transfusion in β-thalassaemia patients. These authors did not mention duration of PaO_2 drop following transfusion; it is also not clear whether such a drop of PaO_2 is confined to thalassaemics.

As our clinical experience on the topic is completely different [2], we reconsidered this issue.

We studied 20 transfusion-dependent β-thalassaemics (age 31 ± 5 years) and 19 patients with anemia of a different etiology matched for age. All thalassaemics were under iron chelation; 12 had been splenectomized. No patient presented with heart failure, whereas 6 were living in a rather hypoxic state. In all subjects, blood was sampled by puncture in a sitting position just before, and 30 min and 24 hr following, transfusion of two blood units. An ABL2 radiometer (Copenhagen, Denmark) was used.

There was no PaO_2 drop at 30-min and 24-hr intervals in all cases studied. Some nonsignificant differences (up to ±8 mm Hg) were within instrumental and individual fluctuations. The relevant PaO_2 mean values (in mm Hg) are depicted in Table I.

According to our findings, it seems that there is no transfusion-related hypoxemia. The findings of Bacalo et al. [1] remain inexplicable, as already mentioned by the authors themselves. However, in any case the implication of microaggregates does not seem plausible for reasons related to the volume of the blood transfused and to the filters in current use. In evaluating the clinical aspects of the procedure, we believe that hypoxia cannot be considered as an obstacle.

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Serum Interleukin-11 in Plasma-Cell Dyscrasias

To the Editor: Intensive research has been devoted to the nature of known and unknown factors able to both stimulate the production of interleukin-6 (IL-6) by the tumor microenvironment and synergize with IL-6 to increase myeloma cell growth. Interleukin-11 (IL-11) is a pleiotropic cytokine that was originally detected in medium conditioned by an interleukin-1α-stimulated primate bone-marrow stromal cell line, PU-34, by its ability to stimulate the proliferation of an IL-6-dependent murine plasmacytoma cell line in the presence of excess neutralizing anti-IL-6 antibodies [1]. IL-11 has also been found to stimulate the T-cell-dependent development of specific immunoglobulin-secreting B cells from murine splenocyte cultures [1] and the differentiation of human B lymphocytes in the presence of accessory cells [2]. In addition, consistent with its in vitro functions, in vivo administration of recombinant human IL-11 to normal mice was found to enhance the generation of immunoglobulin-producing cells [3]. These observations raise interest on the role of IL-11 in plasma-cell dyscrasias, and prompted us to assay this cytokine in the serum of individuals with monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM).

IL-11 was measured in 48 patients with MGUS, 86 patients with MM in various phases of the disease (46 at diagnosis, 18 in plateau phase, and 22 in progression or relapse), and 33 healthy controls. There were 28 men and 18 women (median age 61 years, range 44–83 years) in the untreated myeloma group. According to the Durie and Salmon staging system, 17 were stage I, 19 were stage II, and 10 were stage III; 6 were substage B. Thirty-six patients were IgG, 6 were IgA, 3 were Bence-Jones myeloma, and 1 was nonsecreting myeloma. Patients in plateau phase were considered to be those with partial or complete response after chemotherapy and a stable disease for at least 6 months. The median age of patients from this group was 62.5 years; at time of diagnosis, 10 were stage II and 8 were stage III. The median age of patients with progressing or relapsed disease was 64 years; 5 were originally stage I, 8 stage II, and 9 stage III. Median time to progression or relapse was 14 months (range, 6–27 months).

Measurements of IL-11 in the sera of patients and controls were carried out by enzyme-linked immunoassay (ELISA) instrumentation with amplified sensitivity (V-MAX Reader, Molecular Devices, Menlo Park, CA) equipped with software for the automatic fitting of standard curves according to preset parameters (the four-parameter logistic equation was utilized). A commercially available kit (Quantikine™ Human IL-11, R&D Systems, Minneapolis, MN) was used according to the manufacturer's instructions. Briefly, this assay was based on a double-antibody sandwich method, had a sensitivity limit of 4 pg/ml, a highest intraassay CV of 4.8%, and a highest interassay CV of 8.0%. As reported by the manufacturer, this ELISA is specific for human IL-11 and does not crossreact with other known cytokines.

Measurable levels of IL-11 were found in 2/33 (6.1%) normals, and in 5/48 (10.4%) patients with MGUS, as compared to 14/86 (17.3%) myelomas (P = NS, χ^2 test). It is noteworthy that in MM the cytokine was detected with a comparable frequency in all pathologic stages and phases of the disease (Fig. 1): 2/17 in stage I, 4/19 in stage II, 2/10 in stage III, 3/18 in plateau phase, and 3/22 in progressing or relapsed disease. Besides, IL-11 levels did not correlate with β_2-microglobulin, C reactive protein levels, or erythrosedimentation rate. When comparing outcome of individuals with detectable and

TABLE I. PaO_2 Mean Values (mmHg) Before and Following Transfusions

Patients studied	Before transfusion	After 30 min	After 24 hr
β-thalassaemia (n = 20)	90.7 ± 10.0	90.1 ± 10.5	89.9 ± 10.1
Other anemias (n = 19)	88.3 ± 9.3	86.7 ± 8.0	89.7 ± 6.5